SUPPORT FOR THE AMENDMENTS

Claims 134, 139, 140, 143, 151 to 153, 162, 165 and 177 have been amended to correct typographical errors and/or to further clarify the present invention. Claim 143 has been canceled since the subject matter was introduced in claim 134. Accordingly, no new matter is believed to have been added to the application by the amendments submitted above.

REMARKS

Claims 134, 139-142, 145, 148-155 and 157-158 and 160-177 remain pending.

The rejection under 35 U.S.C. § 112, first paragraph, written description, is respectfully traversed.

The Examiner appears to have taken the position that there is no support in the specification for the term "consisting of" in Claim 153. Applicants respectfully disagree with the Examiner's conclusion for the following reasons.

At least page 22 in the examples describes a construct that reflects the construct recited in Claim 153. This construct is a specific example of the constructs of the present Invention. Thus, Applicants submit that a person skilled in the art would know that the inventors had possession of the claimed invention, by that description.

Furthermore, there is no need for word for word disclosure to fulfill the written description requirement. Even though the term "consisting of" does not appear at page 22 of the specification, it is inherent to the skilled artisan that such a limited construct was in fact disclosed. This is evidenced by the case law of *In re Herschler*, 591 F. 2d 693, 700 (CCPA 1979) where the court stated:

[t]he claimed subject matter need not be described *in haec verba* to satisfy the description requirement.

Moreover, Applicants are enclosing the CNCM deposit No, 1-1663 dated February 1, 1996, which corresponds to the nucleotide construction used by the inventors for producing the claims recombinant protein.

Finally, Figure 2B (legend at page 17 of the specification) shows an immunoblot analysis with human antiserum of the recombinant purified MSP1 P19 fragment from *P. vivax*, as claimed obtained by the inventors from the recombinant construct filed at the C.N,C.M. All of these facts prove that the inventors had possession of the claimed invention.

In view of the foregoing, Applicants submit that the presently claimed invention with respect to the rejected claims does in fact have foundation in the specification in view of the skilled artisan and thus fulfills the written description requirement. Therefore, withdrawal of this ground of rejection is respectfully requested.

The rejection of the claims under 35 U.S.C. § 112, second paragraph, is believed to be obviated by the amendment submitted above.

Claim 159 has been canceled and Claims 162 and 165 have been amended to depend from Claims 176; Claim 177 now has antecedent basis for "at an end of its penetration.."; Claims 139, 140, 143, 145 and 152 have been amended to recite *Plasmodium* parasite; and Claims 145 has been amended to recite *plasmodium cynomolgi*.

Therefore, in view of these amendments, withdrawal of this rejection is respectfully requested.

The rejection of the claims under 35 U.S.C. §103(a) over Longacre (1995) in view of Longacre et al (1994). Those references fail to suggest the claimed composition.

Longacre (1995) discloses the *Plasmodium cynomolgi* merozoite surface protein 1 C-terminal sequence and its homologies with other *Plasmodium* species such as *P. yoelii*, *P. chabaudi*, *P. vivax* and *P. falciparum*. This reference discloses that there is overall 76% sequence homology between *P. cynomolgi* and *P. vivax* and that the percentage of homology varies with the region and that in the EGF domain only *P. cynomolgi* has a Lys to Glu substitution at position 378.

Longacre et al (1994) describe the structure of *P. cynomolgi* MSP1 protein, which was deduced from alignments of its sequence with sequences of MSP1 from *P. falciparum* and *P. vivax*. However, the processing site of the *P. cynomolgi* P19 fragment was not determined with certainty. Two putative processing sites are suggested without knowing which processing site is functional (see, page 108 left; column). Longacre et al (1994)

provides no insight or even suggestion how to choose the part of the protein sequence necessary to express a well-processed P19 fragment.

Neither Longacre (1995) nor Longacre (1994) suggest or disclose making a recombinant protein whose peptide sequence has a leader sequence from Met_1 to Asp_{32} from *Plasmodium vivax* followed by Glu Phe and a 19 kilodalton C-terminal fragment of a surface protein 1 of MSP-1 from *Plasmodium cynomolgi* from Lys_{276} to Ser_{380} as shown in SEQ ID NO: 11, which fragment induces an immune response which can inhibit parasitemia *in vivo* in a host. Furthermore neither reference suggests either alone or in combination to combine a leader sequence from one *Plasmodium* species; i.e., *Plasmodium vivax* with a specific C-terminal 19 kDa fragment of MSP-1 from another *Plasmodium* species; i.e., *Plasmodium cynomolgi*.

Furthermore, the Examiner states that "a recitation of intended use is accorded patentable weight only to the extent that it limits the actual components of a composition."

However, the Examiner's attention is brought to the recent decision of *In re John B. Sullivan and Findlay E. Russell* (CAFC2006-1507) decided August 19, 2007 where the CAFC citing *In re Papesch*, 315 F. 2d 381,391 (CCPA 1963) stated.

> "From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing ... There is no basis in law for ignoring any property in making such a comparison." The issue here is not whether a claim recites a new use, but whether the subject matter of the claim possesses an unexpected use.

Therefore, unexpected properties should also be taken into account when evaluating the recombinant construct (a compound). Applicants submit that the unexpected result of using alum in the vaccine composition should in fact be considered since it was the first time that such an adjuvant was proven to be effective in a recombinant MSP-1 vaccine.

Since the cited prior art does not demonstrate any inducement of an immune response which can inhibit parasitemia *in vivo* in a host in their constructs, it cannot be said that the prior art discloses the features in the rejected claims. Furthermore, the Examples in the specification clearly demonstrate unexpected results due to the high and persistent immune responses achieved.

In view of the foregoing, the claimed composition is not obvious in view of the disclosure of Longacre (1995) and Longacre et al (1994). Accordingly, withdrawal of this ground of rejection is respectfully requested.

The rejection of the claims under 35 U.S.C. §103(a) over Longacre (1995) in view of Longacre et al (1994) and further in view of Holder et al. (U.S. 5,720,959) is respectfully traversed. The cited references fail to suggest the claimed composition.

As discussed above, Longacre (1995) and Longacre et al (1994) fail to suggest the claimed composition.

Holder et al discloses polypeptides having the sequences shown in Figures 1 and 2, which are only individual EGF-like 1 and 2 domains, as well as a combined EGF-like domains of *P. yoelii*. These polypeptides are purportedly used in a vaccine. However, Berghaus et al of record demonstrate that the EGF-like proteins described in Holder et al, which are expressed as fusion proteins in *E. coli* did not induce protection against a challenge of *Aotus nancymai* monkeys. Therefore, no immune response *in vivo* was obtained.

Although some of the examples of Holder et al demonstrate a reduction of parasitemia after challenge with the EGF-like domains, the mice model is not an accepted model for testing blood stage antigens. A P19 from *P. yoelii* is not infectious in humans but only in mice. Thus, the person skilled in the art would realize that one cannot compare the properties of vaccinating compositions of the present invention from a *Plasmodium* parasite infectious for humans with those compositions infectious only in mice.

Moreover, the amount of the challenge dose of 5,000 parasite red blood cells is extremely low and not in the range considering that a single infected hepatocyte usually releases from 20-40,000 merozoites to initiate the blood stage antigen.

Holder et al fail to describe any atomic coordinates and NMR fingerprints as currently recited in Claim 134. These fingerprints are indicative of the precise folded structure of the 19 kilodalton G-terminal fragment used in the vaccinating composition and is indicative of the superior results achieved by the compositions of the present invention.

This is not surprising since the recombinant EGF-like domains produced in Holder et al were produced as fusion proteins in *E. coli*, which fusion proteins do not retain their conformational construct.

The combination of these references fails to suggest the claimed composition, since none of the combined references disclose or suggest a vaccinating composition which can inhibit parasitemia *in vivo* in a host infected with said *Plasmodium* parasite with the claimed atomic coordinates and NMR fingerprints. Accordingly, withdrawal of this rejection is respectfully requested,

The rejection of the claims under 35 U.S.C. § 103(a) over the combined teachings of Chappel and Holder, Miller et al, Longacre et al (1994) and Longacre (1995) is respectfully traversed. These references also fail to suggest the claimed composition.

Chappel and Holder disclose that direct expression of the individual EGF-like domains from MSP1 in *E. coli*, which does not permit to form native immunogenic determinants and that the first domain is the target of growth-inhibitory antibodies.

Chappel and Holder also describe as a control an insect cell product S42AA containing 271 amino acids of the Wellcome strain MSP1, including both EGF-like domains fused to the amino terminal 34 amino acids of MSP1 to provide a signal for secretion.

There is no disclosure in Chappel and Holder that the first EGF-like domain can stimulate an immune response which can inhibit parasitemia *in vivo* in a host infected with *Plasmodium* parasite.

Miller et al is used solely to orient the sequences described in Chappel and Holder.

Longacre (1995) and Longacre et al (1994) were discussed above, and those comments also apply to these references.

The combination of references fails to suggest the claimed composition, since there would be no expectation of success that the currently claimed constructs could in fact inhibit parasitemia *in vivo* in a primate host infected with a *Plasmodium* parasite.

Furthermore, in the present invention there is an amino acid modification in the EGF-like domains (glutamate instead of glutamine in position 1644). But, the disclosure of Holder and Chappell state that by changing one amino acid in the EGF-like domains would in fact affect the binding of monoclonal antibodies and hence no immunogenic activity could be achieved (page 309). Hence, Holder and Chappel actually teach away from the presently claimed invention with this amino acid modification. Moreover the skilled artisan would not make such a modification since there would be no expectation of success.

Based on the foregoing, withdrawal of this rejection is respectfully requested.

The rejection of claims under 35 U.S.C. §103(a) over Chappel et al, Miller et al and Longacre (1994) in view of Longacre et al (1995) and further in view of Holder et al. is respectfully traversed. These references fail to suggest the claimed composition.

Chappel et al, Miller et al Longacre (1994) and Longacre et al (1995) were discussed in detail above, and those comments also apply.

Holder et al describe EGF-like domains from MSP-1 regions and two allelic variants. Although this patent teaches using alum as an appropriate adjuvant, there was no demonstration in the examples that alum could be used as an efficient adjuvant.

Furthermore, Holder et al only demonstrate the efficacy of their recombinant EGF-like fusion protein in a mouse model. However, it was well known in the art that extrapolation from mouse models to human models has not been validated for malaria vaccines. Thus, it cannot be concluded from this patent that inhibition of parasitemia *in vivo* was in fact achieved. Applicants thus submit that the presently claimed invention is unobvious in view of the cited prior art.

Therefore in view of the above, withdrawal of this rejection is therefore respectfully requested.

Applicants respectfully submit that that the present application is in condition for allowance. Early notice to this effect is earnestly solicited.

Respectfully submitted,

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